REMARKS

THE INVENTION.

This invention provides for compositions to increase the half life of a soluble therapeutic viral receptor by permitting it to bind to mucosal inhabiting bacteria. The subject application is a divisional of U.S. Appln. No. 09/549,261, now U.S. Pat. No. 6,365,156, with corresponding method claims.

THE STATUS OF THE CLAIMS.

Claims 17-28 are pending and have been examined. Method of manufacture claims 29-35, 37 and 38 remain withdrawn with the possibility of them being rejoined in accordance with MPEP §821.04 and *In re Ochiai*. The pending claims are directed to compositions. All the pending claims are rejected as obvious over prior art.

REJECTIONS.

Claims 17-20 and 23-28 are rejected under §103(a) as unpatentable over McCormick and Meruelo. McCormick discloses a bispecific antibody for directing phagocytic leukocytes to *Psuedomonas* bacteria to treat bacterial infections in persons with cystic fibrosis. Meruelo teaches the use of a viral specific receptor to increase viral host range for delivery vectors. Applicant respectfully requests reconsideration of this rejection. As explained below, the combination of McCormick and Meruelo fails to set forth a legally sufficient *prima facie* case of obviousness because there is insufficient motivation to modify the McCormick constructs with Meruelo's viral receptors.

As the Examiner knows, a legally sufficient *prima facie* case of obviousness requires an examiner to identify from the prior art: (i) all the salient elements recited in the claim; (ii) an implied or express motivation to combine the elements in the manner recited in the claim; and,

(iii) a reasonable expectation that once combined, the elements would successfully function as described in the specification. Failing to set forth any one of these three prongs is fatal to the rejection.

In the instant situation, there is simply no motivation to combine McCormick with Meruelo. Such motivation cannot come from the applicant's disclosure. Applicant's motivation is to increase the half life of soluble viral receptors which are intended to block viral entry into cells.

In contrast, the motivation for McCormick to create their bispecific antibodies is to overcome opsonin-receptor mismatches in the lungs of cystic fibrosis [CF] patients, who are suffering from infections from the bacteria, *Psuedomonas aeruginosa*. According to McCormick, CF patients over produce the enzyme, elastin, and elastin preferentially cleaves the opsonin iC3b on the bacteria and CR1 on the leukocytes. This creates an opsonin-recepter mismatch that reduces the ability of phagocytes to recognize and attack pathogenic bacteria. The McCormick bispecific antibody was intended to restore the ability of the phagocytes to engulf the bacteria by binding the CR3 (CD18) on the phagocyte and directing it to the bacteria by a second antibody against C3 complement deposited on the bacteria.[1]

In McCormick *et al.*, the underlying purpose of using a bispecific, chimeric binding moiety is to eliminate pathogenic bacteria. That is certainly not the motivation that led to the applicant's invention. Nor does the reliance on Meruelo *et al.*, in combination with McCormick, provide the requisite motivation. Meruelo is attempting to improve viral vector delivery technology by increasing the host range of the viral packages in eukaryote cells. This is done by creating chimeric molecules that permit exogenous viral receptors to bind to novel host cells.

There is little motivation to combine the viral receptors of Meruelo with antibodies against the complement-derived, bacteria bound proteins (opsonin) of McCormick. By combining the McCormick opsonin binding antibodies with a viral receptor, one creates a chimeric, bi-specific binding protein that attracts virus to opsonin covered bacteria. This combination would certainly be inoperable in the context of McCormick's desire to overcome an elastin induced opsonin-receptor mismatch. It is improper to modify a primary prior art teaching with a secondary reference if the combination results in an obvious non-working combination. Moreover, the use of opsonin specific binding partners with viral receptors may actually prevent the phagocytes from recognizing and attacking the bacteria.

Applicant respectfully notes that the Examiner has not adequately articulated any actual motivation in support of the obviousness rejection. The reasoning provided in the Office Action is a mere conclusion. On the last paragraph of page 4 of the outstanding Office Action, the Examiner concludes that placing the bispecific antibodies of McCormack into pharmaceutically acceptable formulations was obvious. Applicant concedes this point.

However, this point relating to formulations of McCormack is not dispositive of the propriety of the obviousness rejection because the *prima facie* case of obviousness requires that an examiner provide motivation for the entire combination of claimed elements. The reasoning on page 4 is silent on whether it was obvious to combine a viral receptor with a mucosal bacteria binding protein.

The Examiner addresses the claimed combination in view of McCormick and Meruelo by stating on page 5,

> It would have been *prima facie* obviousness for one of ordinary skill in the art at the time the invention was made to substitute an antibody to the cell surface receptor CD18, of

[1] The nomenclature makes this a bit more difficult to follow than as set forth above. For example McCormick explains that they used an antibody against C3d because it also binds to C3b and C3b is the opsonin that is found on the bacteria. Thus the second antibody is described here as C3 rather than C3d.

> McCormick *et al.* for a cell surface receptor, such as CD4 or CD21 or Meruelo *et al.* to target tissue-specific cells in the mucosa, such as those that express CD21, or to inhibit viral infection, see column 4, line 58 to column 6, line 61 of Meruelo *et al.*

This statement is the entire basis upon which the motivation prong of the rejection stands. Applicant submits that the above reasoning does not provide an objective scientific reason of motivation for combining McCormick with Meruelo. The quoted sentence is merely a conclusion that it was obvious. The law requires more, and applicant respectfully submits that actual motivation does not exist.

The applicant notes that the Meruelo compositions are stated to have potential as therapeutic agents and that among the recited therapies are methods to inhibit viral infection. However, Meruelo is writing in the context of gene delivery and not in the context of soluble viral receptor therapy. At column 21, lines 4-21, Meruelo discusses the possibility of using their composition to permit viral delivery of anti-viral genes. This is very different than the context of the subject claims and certainly does not motivate or suggest targeting the viral receptors of Merluelo to the opsonin-bound proteins on bacteria.

Having explained that the references do not provide adequate motivation for the outstanding obviousness rejection and the absence of a clear articulation of motivation by the Examiner, applicant further respectfully reminds the Examiner that simplicity is not a legally sufficient basis for rejecting claims as obvious. Merely because one of skill can routinely and mechanically combine the elements of two references is insufficient basis to maintain a *prima facie* case of obviousness. 35 U.S.C. §103(a) expressly states that the manner of making shall not negate patentability.

Finally, the Examiner is reminded that the method claims of the parent application issued in U.S. Pat. No. 6,365,156 because there was a conclusion that the method was non-obvious over

the prior art. Unless the Examiner can identify an alternative and practical use of the claimed composition beyond a mere academic or philosophic inquiry, the rejection should be withdrawn.

A second obviousness rejection was raised over claims 21 and 22 in view of McCormick and Meruelo as applied above in further view of Baba *et al.* Baba teaches the use of C-terminal lysostaphin residues to target hybrid proteins to *Staphylococcus* bacteria. Claims 21 and 22 recite specific bacterial binding proteins and specific species of bacteria for use in the claimed invention. Applicant urges reconsideration in view of the above comments regarding the broader claims and in view of the comments below.

Again, there is simply no motivation to modify the bispecific antibodies of McCormick with the viral binding moieties of Meruelo, and Baba *et al.* does not supply that motivation with its recitation of a specific binding moiety for *Staphlococcus* bacteria.

The Examiner's reasoning is again without an objective statement of why the combination is motivated. She states on page 6 of the Office Action:

> One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the Pa bacterial-specific portion of the bispecific antibody of McCormick *et al.* for the C-terminus of lysostaphin, taught by Baba *et al.* to target *S. aureus* infections in cystic fibrosis patients, see the first paragraph of the introduction of McCormick et al.

While the first paragraph of McCormick may have provided motivation to use lysostaphin for the C3 binding antibody in the context of treating bacterial infection in CF patients, there was simply no motivation to substitute viral-specific binders for McCormick's phagocyte binding antibodies. In the context of McCormick, such a substitution would not work for their intended purpose. Again, applicant relies on the arguments set forth above with regard to McCormick and Meruelo.

Having explained that the combination of all three prior art references does not provide legally adequate motivation to modify the bispecific antibodies of McCormick with the viral

binding components of Meruelo, the rejection of claims 21 and 22 under §103 should be withdrawn.

CONCLUSION

The applicant submits that all the outstanding concerns have been addressed by the rejection and that the examined claims are allowable. Reconsideration of the withdrawn claims is appropriate at this time and applicant respectfully requests rejoinder of manufacturing and system claims 29-35, 37 and 38.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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